REMARKS

Claims 1-25, 27-44 and 46-145 are pending in this application. Claims 1-22, 29, 43, 59-67, 69-84 and 103-106 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 26, 45 and 101 have been cancelled and claims 23, 68, 93 and 94 have been amended. The changes made to the claims by the current amendment, including deletions and additions, are shown herein with deletions designated with a ~~strikethrough~~ and additions underlined. The amended claims do not include new matter as explained below.

Claims 23, 68, 93 and 94 have been amended to clarify that the construct is a recombinant construct. Support for this amendment can be found throughout the Examples and the accompanying Figures.

Claims 23, 93 and 94 have been amended to clarify that the recombinant construct is suitable for identifying a gene expression-modulating element or an agent that modulates the activity of a gene expression modulating element. This amendment is explicitly supported by the original language of the claims.

Claims 23 and 68 have been amended to specify that the intracellular half-life of the recited polypeptide is less than about 3 hours in HeLa cells. This amendment finds support in the specification as originally filed at least in paragraphs [0078], [0079], and Example 14.

From the foregoing, Applicant respectfully asserts that the amendments made herein are fully supported by the specification and do not include new matter.

Rejection Under 35 U.S.C. §101

The Examiner has rejected claims 23, 24, 27, 28, 30, 31, 33-42, 44, 46, 47, 50-58, 68, 85-94, 96, 97, 102, 107, 109-126 and 129-145 under 35 U.S.C. §101 allegedly because the claims are drawn to non-statutory subject matter. The Examiner asserts that the term construct encompasses nucleic acids that exist naturally. Although we do not acquiesce to the Examiner's position because the art-recognized meaning of the term "construct" is that it represents artificially assembled nucleic acid segments, the claims have been amended to refer to "recombinant" constructs in order to expedite favorable prosecution. This amendment, therefore, moots the rejection under 35 U.S.C. §101 and the Examiner is respectfully urged, therefore, to reconsider and withdraw this rejection.

Rejection of Claims Pursuant to 35 U.S.C. §112, Second Paragraph

Claims 23-25, 27, 28, 30-42, 44, 46-58, 68, 85-100 and 107-145 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Examiner asserts that the phrase "identifying elements of this type or agents that modulate their activity" is unclear. This rejection has been rendered moot by the amendment to the claims.

The Examiner has also alleged that the term "half-life" is not just a property of the polypeptide but is also a property of the cell and consequently, "half-life" is a relative term for which neither the specification nor the prior art provide a standard of ascertaining the requisite amount. In response, Applicant has amended the claims to clarify that the intracellular half-life of the polypeptide is measured in HeLa cells, thereby rendering this ground of rejection moot.

Additionally, the Examiner has rejected claims 85, 91-95, 138, 144 and 145 as allegedly being indefinite with regard to the term "AU-rich element." It is alleged that the term "rich" is a relative term for which neither the specification nor the prior art prescribes a standard meaning. Applicant respectfully disagrees.

The term "AU-rich element" (also known as ARE) is a very common and well understood term in the field of RNA and particularly in the field of RNA stability. This term is art-recognized as defining an element that has a high frequency of Adenines and Uracils, which is experimentally determined to reduce the stability of RNA.

An internet search of the term "AU-rich element" using the Google search engine identified about 34,500 hits, of which about 29,400 also contained the word RNA. Of these, about 19,100 also contained the word "stability," which evidences that this term has a well understood meaning.

Significantly, Bakheet *et al* (2001, *Nucleic Acids Research*, **29**(1): 246-254; 2003, *ibid*, **31**(1): 421-443) describe an "AU-rich element database" (ARED). The existence of such a database shows that the terms "ARE" and "AU-rich element" are not only well understood terms but that the presence/absence of an ARE in a particular construct can be determined through comparison to the database.

In addition, the United States Patent and Trademark Office has issued patents with claims that recite "AU-rich element" (see, *e.g.*, U.S. Patent Nos. 6,852,531; 6,706,491 and 6,627,398).

Accordingly, it is respectfully submitted that the term "AU-rich element" has a clear meaning in the art and the Examiner is respectfully urged, therefore, to reconsider and withdraw this ground of rejection.

Rejections of Claims Pursuant to 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 23-25, 27, 28, 30-42, 44, 46-58, 68, 85, 87-94, 96-100, 107-123, 135-138 and 140-145 as allegedly failing to comply with the written description requirement. Specifically, the Examiner asserts that the specification only teaches a variety of genes and discloses several elements that function to modulate transcript stability such as from *c-fos* and found in SEQ ID NO: 19. In addition, it is asserted that it is unclear if all 3'UTR sequences comprise the elements required to modulate stability or simply a subset of these genes such as those disclosed. The Examiner then goes on to allege that neither the prior art nor the specification teaches that any of these elements mediate RNA stability and that given the large size and diverse nature of "RNA elements" and the inability to determine which will also possess the ability to modulate the stability of a transcript in a construct, the invention must be empirically determined. On this basis, the Examiner concludes that the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show that Applicant was in possession of the claimed genus. Applicant strongly disagrees with the Examiner's position, which is neither supported by fact nor by precedent.

The rejected claims refer to a "RNA element that modulates the stability of a transcript." The specification defines RNA destabilizing elements in paragraph [0170] *inter alia* as "a sequence of nucleotides which reduces the intracellular half-life of a RNA transcript." Illustrative RNA destabilizing elements from various genes are disclosed in paragraph [0175] including those from *c-fos*, *c-jun*, *c-myc*, *GM-CSF*, *IL-3*, *TNF-alpha*, *IL-2*, *IL-6*, *IL-8*, *IL-10*, *Urokinase*, *bcl-2*, *SGLT1* (Na(+)-coupled glucose transporter), *Cox-2* (cyclooxygenase 2), *IL8*, *PAI-2* (plasminogen activator inhibitor type 2), *beta1-adrenergic* receptor and *GAP43* (5'-UTR and 3'-UTR) genes. Additionally, the same paragraph discloses that:

> "RNA destabilizing sequences may be selected from AU-rich elements (AREs) and/or U-rich elements (UREs), including but not limited to single, tandem or multiple or overlapping copies of the nonamer UUAUUUA(U/A)(U/A) [SEQ ID NO:2] (where U/A is either an A or a U) (Lagnado et al 1994) and/or the pentamer AUUUA [SEQ ID NO:3] (Xu et al 997) and/or the tetramer AUUU [SEQ ID NO:4] (Zubiaga et al. 1995). The term "tandem copies" allows for both duplication and/or non-duplication of one or more of the outer nucleotides. For example, tandem copies of the pentamer AUUUA

> [SEQ ID NO:3] , includes sequences such as AUUUAUUUAUUUA [SEQ ID NO:5] as well as AUUUAAUUUAAUUUA [SEQ ID NO:6] . RNA destabilizing elements have also been described for example from phosphoenolpyruvate carboxy kinase mRNA (PEPCK), the Drosophila Bicoid gene, the human thioredoxin gene, heat stable antigen gene and soybean 10A5 gene."

Non-limiting RNA destabilizing sequences are listed in SEQ ID NOs: 1-23. Accordingly, there are numerous RNA elements disclosed in the instant specification and in the prior art, which are art-recognized for decreasing the stability of RNA.

It appears that the Examiner has construed that the specification only discloses RNA elements that are isolated from the 3'UTR of various genes. This is incorrect. For example, the tandem or multiple overlapping copies of the nonamer UUAUUUA(U/A)(U/A), the pentamer AUUUA and the tetramer AUUUU as described in paragraph [0175] are entirely synthetic. Also, Shyu *et al.* (1989, *Genes and Development*, **3**: 60-72), which is incorporated by reference in the specification discloses that the *c-fos* transcript is targeted for rapid decay by two distinct mRNA degradation pathways and defines RNA destabilizing elements contained in both the *3'UTR* and *coding sequence* of the *c-fos* gene. Reference also may be made to Newman *et al.* (1993, *The Plant Cell*, **5**:701-714), which is also incorporated by reference in the present specification, and which discloses examples of *5'UTR* destabilizing elements. Additionally, the specification discloses GAP43 5'UTR as an example of a 5'UTR destabilizing element at least at page 33, line 32 (paragraph [0175]) and page 52, line 18 (paragraph [0266]). Accordingly, the specification is replete with different examples of RNA destabilizing elements that are not derived from the 3'UTRs of genes.

Precedent illustrates that the determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in a particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter (see, for example, in *Re Wallach*, 378 F.3d 1330, 1333-13334 (Fed. Cir. 2004) (an amino acid sequence supports "the entire genus of DNA sequences" that can encode the amino acid sequence because "the state of the art has developed" such that it is a routine matter to convert one to the other); *University of Rochester*, 358 F.3d at 925 (considering whether the patent disclosed the compounds necessary to practice the claimed method, given the state of technology); *Singh* -v- *Brake*, 317 F.3d 1334, 1343 (Fed. Cir. 2002) (affirming adequacy of disclosure by distinguishing

precedent in which the selection of a particular species within the claimed genus had involved "highly unpredictable results").

The constructs of the present invention are produced by selecting and combining known RNA destabilizing elements with known polypeptide-encoding polynucleotides, using known DNA-linking procedures. Significantly, therefore, the present invention is not directed to discovering which nucleic acid segments encode RNA destabilizing elements, for that is in the prior art. Instead, the invention is predicated upon the novel combination of protein-encoding polynucleotides and RNA destabilizing elements to achieve a novel result; *i.e.*, improved temporal correlation between protein expression and promoter activity, *e.g.*, by reducing the time lag between decreased promoter activity and decreased levels of a corresponding expression product or by reducing the steady-state level of the expression product such that increased promoter activity results in a larger and/or faster increase in levels of the expression product relative to that present before the increase in promoter activity (see paragraph [0167] of the instant specification). When the prior art includes the structural information used to produce the claimed constructs, precedent does not set a *per se* rule that the information must be determined afresh.

Thus, in view of the specific examples and general teachings in the present specification and the known science, it is respectfully submitted that the instant specification teaches a novel combination of known DNA sequences of known function and not a genus of elements whose structure and function were not known in the art. Accordingly, the Examiner has erred in requiring the Applicant to teach the structural variation across the genus of RNA destabilizing elements when it is clear that the art was replete with nucleic acid sequences with this function at the filing date of the present application.

Applicants' position is supported by the recent decision of the United States Courts of Appeals for the Federal Circuit decision in *Capon* v. *Eshhar* 418 F.3d 1349, 1360 (Fed. Cir. 2005). This decision involved an interference proceeding in which the commissioner of patents was party to the proceeding, and thus, is fully binding on the USPTO. The USPTO had taken the position that the written description must include a listing of the specific nucleotide sequence of claimed DNA. However, on appeal, the CAFC reversed this position of the USPTO, finding that a written description did not require a recitation in the specification of the nucleotide sequence of the claimed DNA when the portions of the sequence were already known. When, as in the

present invention, the prior art includes the nucleotide information, the case law does not require that the information must be presented again the specification.

The Examiner is respectfully urged, therefore, to reconsider and withdraw the rejection of claims pursuant to 35 U.S.C. §112, first paragraph.

Rejection of Claims under 35 U.S.C. §102

Zhao *et al.* (Methods in Enzymology, 1999, **302**: 32-38)

The Examiner has rejected claims 68, 107-118, 120-122, 125, 126, 129-135, 138 and 140 under 35 U.S.C. §102(b) as allegedly being anticipated by Zhao *et al.*, as evidenced by Eurekah Bioscience (Eurekah.com, "Degradation of RNA in prokaryotes") as further evidenced by Kassler *et al.* (*Nucleic Acids Research*, 1986, pages 4939-4952). The Examiner alleges that Zhao *et al.* teach a construct comprising in operable linkage a polynucleotide that encodes a polypeptide that has a half-life of less than about three hours operably linked to a SV40 polyadenylation sequence. It is further alleged that the polyadenylation sequence encodes a RNA element that modulates the stability of a transcript encoded by the polynucleotide. Specifically, the Examiner seems to suggest that a poly(A) tail is a RNA destabilizing element, which is encoded by a polyadenylation sequence and cites the Eurekah Bioscience article in support. Applicant respectfully disagrees.

The SV40 polyadenylation sequence does not lead to RNA destabilization in eukaryotic cells (*e.g.*, the control constructs used to generate the experimental data in the instant specification contain the SV40 polyadenylation signal but did not show RNA destabilization). Indeed, the SV40 polyadenylation signal is widely used in eukaryotic cells because it yields high RNA and protein levels; features that would not be possible if it led to RNA destabilization. It is interesting to note from the Eurekah Bioscience article that the poly(A) tail has a different function and effect in bacteria (where polyadenylation signals are not normally present in genes).

Significantly, the claims recite "a construct comprising...a nucleic acid sequence that *encodes* a RNA element that modulates the stability of a transcript" and neither the SV40 polyadenylation signal nor the poly(A) tail fall within the scope of such claims. This is because a polyadenylation sequence does not *encode* a poly(A) tail. Indeed, the poly(A) tail is not encoded at all by the RNA or DNA. If it were, then every gene would end with a long stretch of several

hundred Adenines, which clearly is not the case. Rather, the polyadenylation sequence is a signal that recruits various enzymes that cleave the RNA and add the poly(A) tail post-transcriptionally.

Indeed, in the field of nucleic acids, the word "encodes" has a clear and concise meaning. For example, CAUG in the RNA is encoded by CATG on the sense strand of the DNA (or GTAC on the antisense strand). Poly(A) tails are not encoded by any part of the gene or RNA and therefore do not fall within the scope of the claims.

Andersen *et al.*, (1998, *Applied and Environmental Microbiology*, **64**: 2240-2246)

The Examiner has rejected claims 68, 108, 109, 111-115, 117, 118, 120-122, 125, 126 and 129-133 under 35 U.S.C. §102(b) as allegedly being anticipated by Andersen *et al.* as evidenced by the pUC18 map and Herrero *et al.* (1990, *J. Bacteriol*, **172**(11): 6557-6567). The Examiner alleges that Andersen *et al* teach a construct comprising in operable linkage a polynucleotide that encodes a polypeptide having a half-life of less than about three hours operably linked to transcriptional terminators, which in the Examiner's view, equate to nucleic acid sequences that encode RNA elements that modulate the stability of a transcript encoded by the polynucleotide. The Examiner is respectfully mistaken.

Andersen *et al.* do not use a eukaryotic polyadenylation signal but instead, use a bacterial transcriptional terminator, which does not lead to polyadenylation of polynucleotides. No evidence was adduced by the Examiner to suggest that such termination sequences have any effect on RNA stability. Additionally, none of the cited references discloses that any nucleic acid sequence of the disclosed vectors encodes a RNA element that destabilizes transcripts. Accordingly, the Examiner is respectfully urged to reconsider and withdraw this ground of rejection.

Leclarc *et al.*, (2000, *Biotechniques*, **29**: 590-601)

Claims 68, 93, 94, 96-100, 102, 107-118, 120-122, 125, 126, 129-136, 138 and 140-145 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Leclarc *et al.*, as evidenced by Eurekah Bioscience (*supra*), as further evidenced by Kessler *et al.* (*supra*) and as further evidenced by Clontech (pMAMneo map).

This ground of rejection is analogous to the one relating to Zhao *et al.* Accordingly, our arguments in respect to Zhao *et al.* also apply to this citation.

Mateus and Avery, (2000, *Yeast*, **16**: 1313-1323)

The Examiner has rejected claims 23-25, 27, 28, 30-37, 39-41, 46, 47, 50-55, 68, 85, 87, 107-118, 120-122, 125, 126, 129-134, 138 and 140 under 35 U.S.C. §102(b) as allegedly being anticipated by Mateus and Avery as evidenced by Wach *et al.*, (1997, *Yeast*, **13**: 1065-1075), as further evidence by Wach *et al.*, (1994, *Yeast*, **10**: 1793-1808), as further evidenced by Bennetzen and Hail (1982, *J. Biol. Chem.*, **267**(6): 3018-3025), and as further evidenced by Eurekah Bioscience (*supra*). Again, the Examiner is of the view that the Adh1 terminator in constructs disclosed by Mateus and Avery, represents a polyadenylation signal that encodes a RNA destabilizing element. This is erroneous for the reasons set forth above.

The Examiner also appears to be alleging that the Adh1 polyadenylation sequence comprises an AU-rich element and draws particular attention to Figure 4 of Bennetzen and Hail. However, as explained above, not all sequences that have a string of Adenines and Uracils are effective in destabilizing RNA. This is because AU-rich elements have particular structures that are experimentally determined as being RNA destabilizing. Accordingly, none of Mateus and Avery, Wach *et al.* or Bennetzen *et al.* discloses RNA destabilizing elements and thus, even when combined, they fail to disclose each and every element recited in the claims. As such, Applicant respectfully urges the Examiner to reconsider and withdraw this ground of rejection.

Rejection of Claims Pursuant to 35 U.S.C. §103

The Examiner has used the references discussed above ("the alleged 102(b) prior art), which allegedly anticipate the claimed invention, in combination with other references in an attempt to render obvious various dependent claims not anticipated by the alleged 102(b) prior art. However, as discussed above, the alleged 102(b) prior art do not meet the limitations of the claims. Accordingly, a *prima facie* showing of obviousness cannot be established based on these references. The additional citations do not remedy the deficiencies of the alleged 102(b) prior art and consequently the obviousness rejections must also fail. For these reasons, Applicant respectfully urges the Examiner to reconsider and withdraw the rejection of claims pursuant to 35 U.S.C. §103(a).